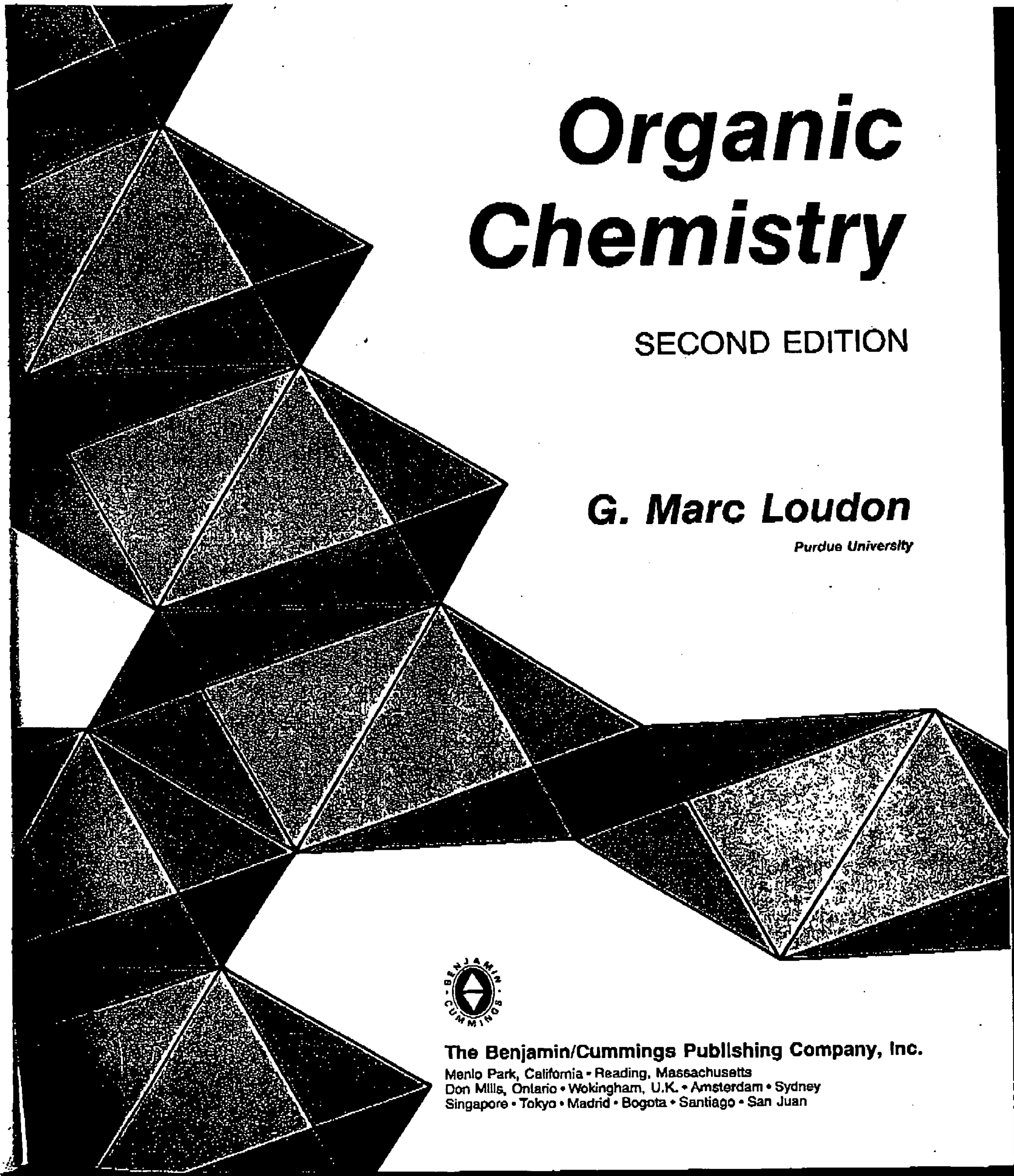


Organic Chemistry

SECOND EDITION

G. Marc Loudon

Purdue University

The Benjamin/Cummings Publishing Company, Inc.
Menlo Park, California • Reading, Massachusetts
Don Mills, Ontario • Wokingham, U.K. • Amsterdam • Sydney
Singapore • Tokyo • Madrid • Bogota • Santiago • San Juan

Sponsoring Editor: *Diane Bowen*
Production Supervisor: *Karen Gulliver*
Production and Art Coordination: *Pat Waldo and Deborah Gale/Partners in Publishing*
Copy Editor: *Carol S. Kinney*
Developmental Art Editor: *Andre Newman*
Text and Cover Designer: *Michael Rogondino*
Illustrators: *Linda Harris-Sweezy, J & R Technical Services, George Klatt, Linda McVay, Carol Verbeeck*
Proofreader: *Steve Sorensen*
Compositor: *York Graphic Services*

Library of Congress Cataloging-in-Publication Data

Loudon, G. Marc.
Organic chemistry.

Includes index.
1. Chemistry, Organic. I. Title.
QD251.2.L68 1988 547 87-29996
ISBN 0 8053-6643-1

Permission for publication herein of Sadtler Standard Spectra® has been granted, and all rights are reserved, by Sadtler Research Laboratories, Division of Bio-Rad Laboratories, Inc.

Additional credits are listed starting on page C-1.

Copyright © 1988 by Benjamin/Cummings Publishing Company, Inc.
© 1984 by Addison-Wesley Publishing Company, Inc.
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the publisher.
Printed in the United States of America. Published simultaneously in Canada.

DEFGHIJ-VH 89

The Benjamin/Cummings Publishing Company, Inc.
2727 Sand Hill Road
Menlo Park, California 94025

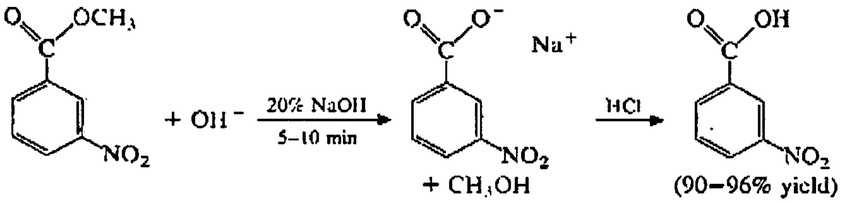
(Compare this reaction with addition to the carbonyl group of an aldehyde or ketone.) The resulting addition products are stable in some cases; but in most of the reactions we shall study, they react further.

Like aldehydes and ketones, carboxylic acid derivatives undergo certain reactions involving the α-carbon. The α-carbon reactions of all carbonyl compounds are grouped together in Chapter 22. The reactivity of amides at the nitrogen is discussed in Sec. 23.11C.

21.7 HYDROLYSIS OF CARBOXYLIC ACID DERIVATIVES

A. Hydrolysis and Cleavage of Esters

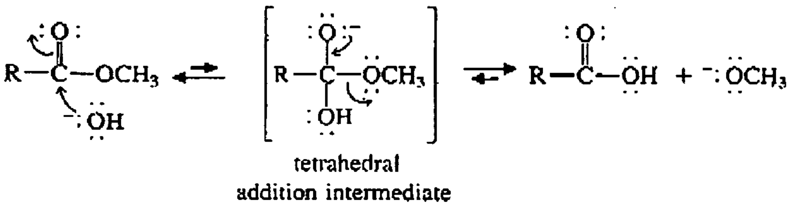
Saponification of Esters All carboxylic acid derivatives have in common the fact that they undergo *hydrolysis* (a cleavage reaction with water) to yield carboxylic acids. One of the most important of these reactions is the hydrolysis of esters in base to yield carboxylate salts and alcohols. The carboxylic acid itself is formed when mineral acid is subsequently added to the reaction mixture.



(21.9)

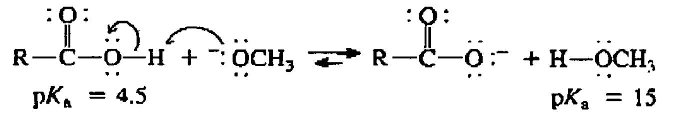
Ester hydrolysis in aqueous hydroxide is called **saponification** because it is used in the production of soaps from fats (Sec. 21.12B). Despite its association with fatty-acid chemistry, the term *saponification* is sometimes used to refer to hydrolysis in base of any acid derivative.

The mechanism of ester saponification involves attack by the nucleophilic hydroxide anion to give a tetrahedral addition intermediate from which an alkoxide ion is expelled.



$$\mathrm{R{-}\overset{\overset{:\ddot{O}:}{\|}}{C}{-}OCH_3} + {}^-{:}\ddot{O}H \rightleftharpoons \left[\mathrm{R{-}\underset{:\ddot{O}H}{\overset{:\ddot{O}:^-}{C}}{-}\ddot{O}CH_3}\right] \rightleftharpoons \mathrm{R{-}\overset{\overset{:O:}{\|}}{C}{-}\ddot{O}H} + {}^-{:}\ddot{O}CH_3 \qquad (21.10a)$$

The alkoxide ion thus formed (methoxide in the above example) reacts with the acid to give the carboxylate salt and the alcohol.

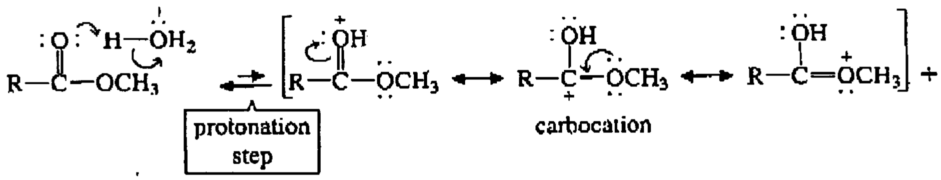


$$\underset{\mathrm{p}K_a\ =\ 4.5}{\mathrm{R{-}\overset{\overset{:O:}{\|}}{C}{-}\ddot{O}{-}H}} + {}^-{:}\ddot{O}CH_3 \rightleftharpoons \mathrm{R{-}\overset{\overset{:O:}{\|}}{C}{-}\ddot{O}{:}^-} + \underset{\mathrm{p}K_a\ =\ 15}{\mathrm{H{-}\ddot{O}CH_3}} \qquad (21.10b)$$

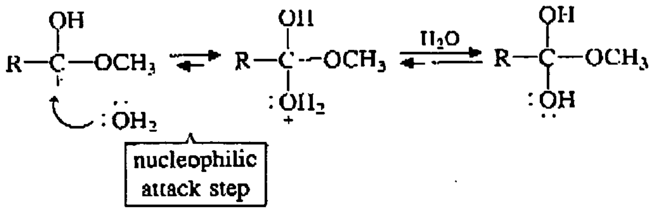
The equilibrium in this reaction lies far to the right because the carboxylic acid is a much stronger acid than methanol. Once again we see LeChatelier's principle at work: the reaction in Eq. 21.10b removes the carboxylic acid from the equilibrium in Eq. 21.10a as its salt and thus drives the hydrolysis to completion. Hence, *saponification is effectively irreversible.* Although an excess of hydroxide ion is often used as a matter of convenience, many esters can be saponified with just one equivalent of ^{-}OH. The equilibrium for saponification is so favorable that it can be conducted in an alcohol solvent, even though alcohol is one of the saponification products.

Acid-Catalyzed Ester Hydrolysis Since esterification of an acid with an alcohol is a reversible reaction (Sec. 20.8A), esters can be hydrolyzed to carboxylic acids in aqueous mineral acid. In most cases this reaction is slow and must be carried out with an excess of water, in which most esters are insoluble. Saponification, followed by acidification, is a much more convenient method for hydrolysis of most esters because it is faster, it is irreversible, and it can be carried out not only in water, but also in a variety of solvents—even alcohols.

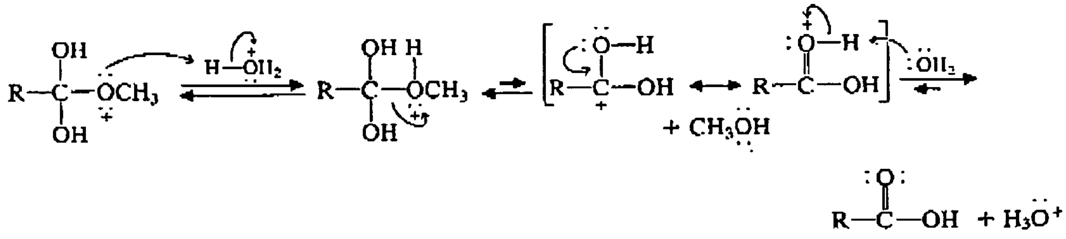
Let us contrast the mechanisms of ester hydrolysis in acid and base. By the principle of microscopic reversibility (Sec. 10.1A), the mechanism of acid-catalyzed hydrolysis is the exact reverse of acid-catalyzed esterification (Sec. 20.8A):



(21.11a)



(21.11b)

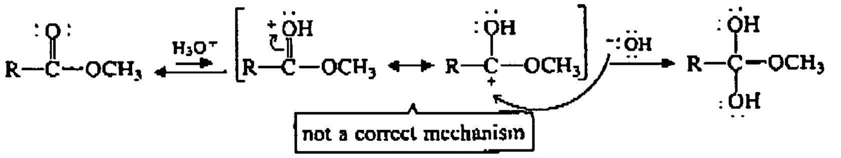


(21.11c)

When a strong acid is present, the carbonyl oxygen is protonated. This protonation gives the carbonyl carbon more carbocation character (Eq. 21.11a). Because there is considerable positive charge on the carbonyl carbon, it is readily attacked by the relatively weak Lewis base (nucleophile) water (Eq. 21.11b). From the saponification mechanism in Eq. 21.10, we see that in base, the carbonyl oxygen is *not* protonated.

and the carbonyl carbon therefore has *less* carbocation character. Hence it takes a stronger base than water—hydroxide ion—to react with the carbonyl group (Eq. 21.10a).

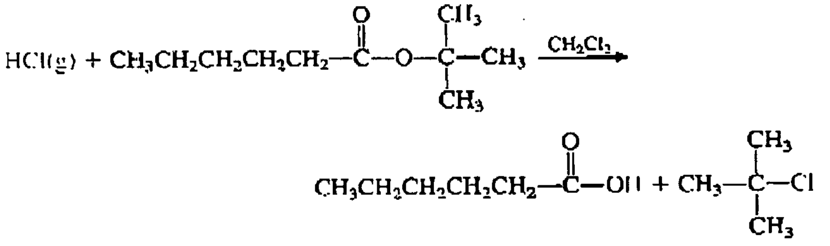
Some students try to combine elements of the acidic and basic mechanisms by protonating the carbonyl group and then attacking it with hydroxide.



(21.12)

Although this mechanism looks as if it ought to be especially attractive, it is not correct because *a solution cannot be acidic enough to protonate the carbonyl oxygen and basic enough to contain substantial hydroxide ion at the same time.* Reactions that require relatively strong acids (such as H_3O^+) typically involve relatively weak bases (such as H_2O); reactions that require relatively strong bases (such as OH^-) involve relatively weak acids (such as H_2O). This same point was made in Sec. 19.7A, where we discussed mechanisms of carbonyl-addition reactions.

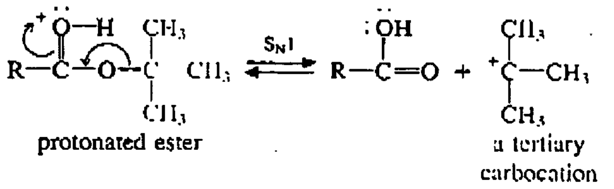
Acidic Cleavage of Tertiary Esters As we have just seen, the hydrolysis of ordinary esters in aqueous acid involves attack of water at the carbonyl group. Esters derived from *tertiary alcohols,* such as *t*-butyl esters, are also converted rapidly by acid into carboxylic acids, but by a different mechanism. Consider, for example, cleavage of the following *t*-butyl ester by anhydrous HCl.



$$HCl(g) + CH_3CH_2CH_2CH_2CH_2-\overset{O}{\overset{\|}{C}}-O-\overset{CH_3}{\underset{CH_3}{C}}-CH_3 \xrightarrow{CH_2Cl_2} CH_3CH_2CH_2CH_2CH_2-\overset{O}{\overset{\|}{C}}-OH + CH_3-\overset{CH_3}{\underset{CH_3}{C}}-Cl \quad (21.13)$$

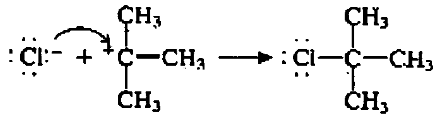
As this example illustrates, conversion of tertiary esters into carboxylic acids does not even require water (although water *can* be present).

The first step in the mechanism of this reaction is the same as in mechanisms involving acid-catalyzed carbonyl substitution: protonation of the ester carbonyl oxygen, as in Eq. 21.11a. However, here the similarity to carbonyl substitution ends. The protonated ester undergoes a simple S_N1 reaction to give the carboxylic acid and a relatively stable tertiary carbocation:



(21.14a)

This cation undergoes the usual carbocation reactions—for example, attack by a nucleophile.



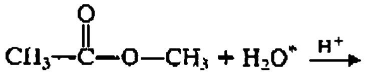
$$:\ddot{\underset{..}{Cl}}:^- + {}^+C(CH_3)_3 \longrightarrow :\ddot{\underset{..}{Cl}}—C(CH_3)_3 \qquad (21.14b)$$

Notice that cleavage of tertiary esters by this mechanism involves breaking the *alkyl-oxygen bond* (Eq. 21.14a). In contrast, acid-catalyzed ester hydrolysis by the carbonyl substitution mechanism involves breaking the *carbonyl-oxygen bond* (Eq. 21.11c). Thus, the mechanism of tertiary ester cleavage does not conveniently fit into any of the categories discussed in Sec. 21.6. Rather, it is more like the S_N1 mechanism for substitution in a tertiary alcohol. (Compare Eqs. 21.14a,b with Eqs. 10.14a–c.) Esters of primary and secondary alcohols do not cleave by this mechanism, because the cations that would be formed are much less stable.

Problem

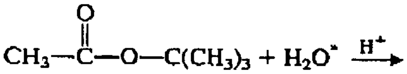
8 Give the products of the following reactions, including the fate of the ^{18}O isotope ($O^* = {}^{18}O$):

(a)



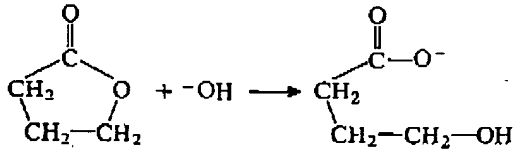
$$CH_3—\overset{\overset{O}{\|}}{C}—O—CH_3 + H_2O^* \xrightarrow{H^+}$$

(b)



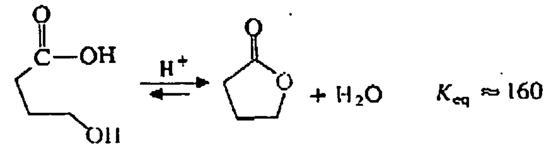
$$CH_3—\overset{\overset{O}{\|}}{C}—O—C(CH_3)_3 + H_2O^* \xrightarrow{H^+}$$

Hydrolysis and Formation of Lactones Because lactones are cyclic esters, they undergo many of the reactions of esters, including saponification. Saponification converts a lactone completely into the salt of the corresponding hydroxy acid.

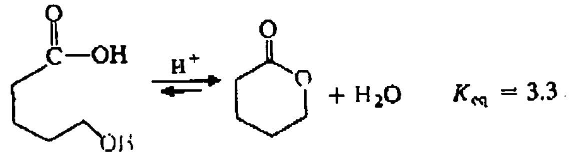


(21.15)

Upon acidification, the hydroxy acid forms. However, *if a hydroxy acid is allowed to stand in acidic solution, it comes to equilibrium with the corresponding lactone.* The formation of a lactone from a hydroxy acid is nothing more than an *intramolecular* esterification (esterification within the same molecule) and, like esterification, the lactonization equilibrium is acid catalyzed.

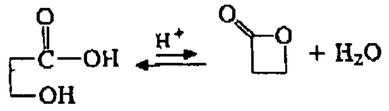


(21.16)



(21.17)

As the examples in Eqs. 21.16 and 21.17 illustrate, lactones containing five- and six-membered rings are favored at equilibrium over their corresponding hydroxy acids. Although lactones with ring sizes smaller than five or larger than six are well known, they are less stable than their corresponding hydroxy acids. Consequently, the lactonization equilibria for these compounds favor instead the hydroxy acids.

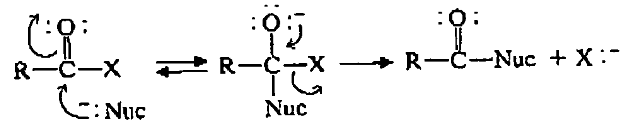


(almost no lactone present at equilibrium) (21.18)

B. Mechanisms of Substitution at the Carbonyl Group

The mechanisms of ester hydrolysis reactions in acid and base are worth special attention for a very important reason: *Most of the carbonyl-substitution reactions we shall study—not only hydrolysis reactions, but other substitution reactions as well—proceed by analogous mechanisms.* Hence, if we understand ester hydrolysis, we understand most of the other carbonyl-substitution reactions that we shall encounter.

Let us generalize: substitution reactions at the carbonyl group occur by two types of mechanisms. Under *basic* conditions, a nucleophile (Nuc : ⁻) attacks the carbonyl carbon to give a tetrahedral addition intermediate in which the carbonyl oxygen assumes a negative charge. The leaving group X : ⁻ is then expelled from the tetrahedral intermediate.



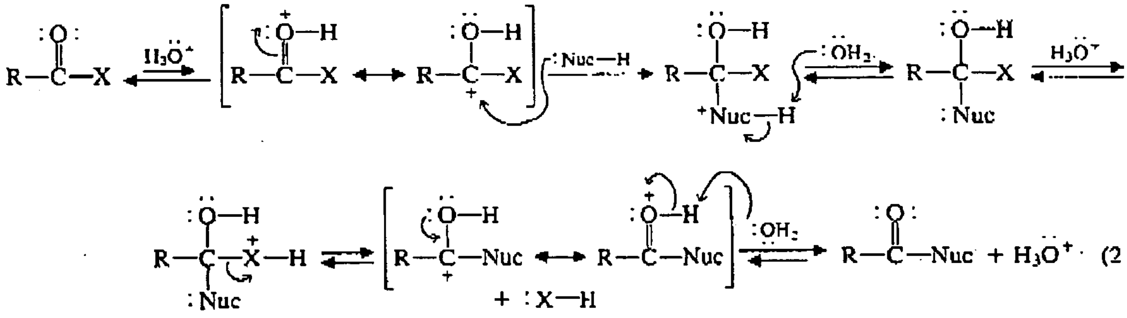
tetrahedral addition intermediate

(21.19)

In ester saponification, for example, ⁻ : Nuc is ⁻OH, and X : ⁻ is the ⁻OR group of the ester.

Under *acidic* conditions, the carbonyl is first protonated. This protonation imparts cationic character to the carbonyl carbon. This carbon is then attacked by a relatively weak base : Nuc—H to form a tetrahedral addition intermediate. After proton transfer to the leaving group —X, it is expelled as H—X.

BEST AVAILABLE COPY



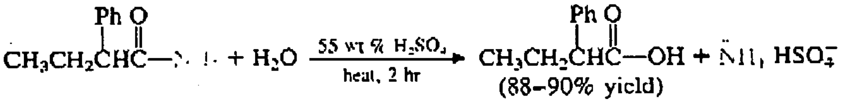
(21.20)

In acid-catalyzed ester hydrolysis, for example, :Nuc—H is HO—H, and X—H is the alcohol product RO—H.

Notice how each subsequent carbonyl substitution reaction that we consider falls into one of these categories.

C. Hydrolysis of Amides

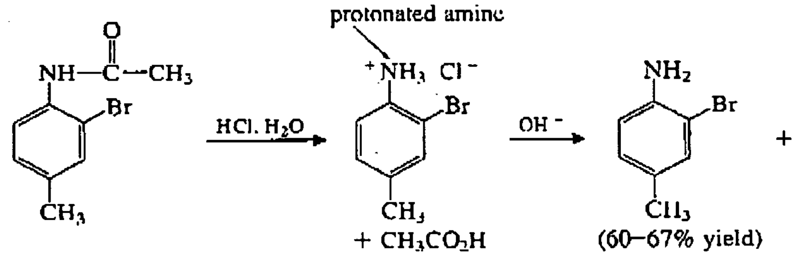
Amides can be hydrolyzed to carboxylic acids and ammonia or amines by heating them in acidic or basic solution.



$$CH_3CH_2\overset{Ph}{C}H\overset{O}{\overset{\|}{C}}—NH_2 + H_2O \xrightarrow[\text{heat, 2 hr}]{\text{55 wt \% } H_2SO_4} CH_3CH_2\overset{Ph}{C}H\overset{O}{\overset{\|}{C}}—OH + \overset{+}{N}H_4\ HSO_4^- \quad (21.21)$$

(88–90% yield)

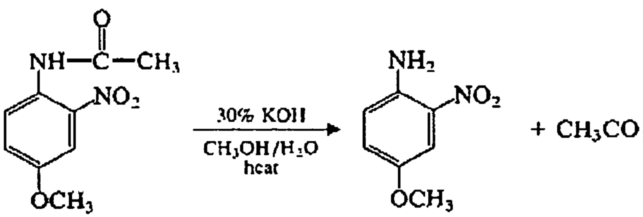
In acid, protonation of the ammonia or amine by-product drives the hydrolysis equilibrium to completion. The amine can be isolated, if desired, by addition of base to the reaction mixture following hydrolysis.



(60–67% yield)

(21.22)

Hydrolysis of amides in base is analogous to saponification of esters. In base, the reaction is driven to completion by formation of the carboxylic acid salt.



(95–97% yield)

(21.23)